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14 April 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TARGETING ENZYMES OF THE tRNA SPLICING PATHWAY FOR IDENTIFICATION OF ANTI-FUNGAL AND/OR ANTI-PROLIFERATIVE MOLECULES

(57) Abstract: The present invention relates to a method for screening and identifying compounds that modulate the activity of one or more components in the tRNA splicing pathway. In particular the invention relates to a method for screening and identifying compounds that modulate the activity tRNA splicing endonuclease and/or tRNA splicing ligase. The invention provides assays for the identification of compounds that inhibit animalia tRNA splicing endonuclease and/or animalia tRNA splicing ligase. The invention also provides assays for the identification of compounds that inhibit fungal tRNA splicing endonuclease and/or fungal tRNA splicing ligase. The methods of the present invention provide a simple, sensitive assay for high-throughput screening of libraries of compounds to identify pharmaceutical leads useful for treating and/or preventing cancer and/or fungal infections.



WO 2004/087884 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/09590

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 61/00; C12Q 1/00; G01N 33/566, 33/573, 33/574

US CL : 435/ 4, 6, 7.2, 7.21, 41, 69.2, 91.3, 183 ; 514/ 1, 2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/ 4, 6, 7.2, 7.21, 41, 69.2, 91.3, 183 ; 514/ 1, 2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,726,195A (HILL et al.) 10 March 1998, see entire patent.	18-19
X	US 6,446,032 B1 (SCHIMMEL) 03 September 2002, see entire patent document.	20-21
X	WO 02/083837 A1 (PTC CORPORATION, INC.) 24 October 2002, see entire document, especially abstract, examples and claims.	18-21
— Y		1-24
X	WO 02/083953 A1 (PTC CORPORATION, INC.) 24 October 2002, see entire document, especially abstract, examples and claims.	18-21
— Y		1-24
X	WO 01/25486 A1 (UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY) 12 April 2001, see entire document, especially abstract, examples and claims.	18-21
— Y		1-24

☒ Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

15 December 2004 (15.12.2004)

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27 JAN 2005

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/09590

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Rélevant to claim No.
X — Y	GREER, C.L. Assembly of a tRNA Splicing Complex: Evidence for Concerted Excision and Joining Steps in Splicing In Vitro. Molecular and Cellular Biology. February 1986, Vol. 6, No. 2, pages 635-644, see entire article, especially Fig. 1, pages 638-642.	1, 7, 8, 11, 13, 15 and 17 ----- 1-24
Y	LI et al. Crystal Structure and Evolution of a Transfer RNA Splicing Enzyme. Science. 10 April 1998, Vol. 280, No.10, pages 279-284, see entire article.	1-24
Y	HYDE-DERUYSCHEER et al.. Detection of Small-Molecule Enzyme Inhibitors With Peptides Isolated From Phage-Displayed Combinatorial Peptide Libraries. Chemistry & Biology. 2000, Vol. 7, No. 1, pages 17-25, see entire article, especially Abstract, Table 1 and pages 23-24.	1-24
A	ABELSON et al. tRNA Splicing. J. Biol. Chem. 22 May 1998, Vol. 273, No. 21, pages 12685-12688, see entire article.	1-24
A	TROTTA et al. The Yeast tRNA Splicing Endonuclease: A Tetrameric Enzyme With Two Active Site Subunits Homologous To The Archaeal tRNA Endonucleases. Cell. 13 June 1997, Vol. 89, pages 849-858, see entire article.	1-24
A	VAUGHAN et al. Methionine In and Out of Proteins: Targets for Drug Design. Current Medicinal Chemistry. 2002, Vol. 9, No. 3, pages 385-409, see entire article.	1-24

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/09590

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 25
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/09590

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-3, 7(in part), 8, 11-14(in part), 15, 17(in part), 22 and 23-24(in part), drawn to assaying for an antifungal compound that inhibits fungal tRNA splicing ligase.

Group II, claim(s) 4-6, 7(in part), 9-10, 11-14(in part), 16, 17(in part) and 23-24 (in part) drawn to assaying for an anti-proliferative compound that inhibits animal tRNA splicing ligase.

Group III, claim(s) 18-19, drawn to preventing/treating a fungal infection by administering an antifungal compound identified by the Group I method.

Group IV, claim(s) 20-21, drawn to treating a proliferative disorder by administering an anti-proliferative compound identified by the Group II method.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the methods of Groups I and II are distinctly different methods drawn to different method objectives and utilize different sources of enzymes. The antifungal and antiproliferative compounds of Groups III and IV derived from the Group I and II methods do not represent a "special" technical feature since antifungal and antiproliferative compounds are known in the art. See e.g. see RNA binding "small molecule" compounds disclosed in WO 02/083953A1; WO 02/083837A1; and WO 01/25486A1.

Continuation of B. FIELDS SEARCHED Item 3:
WEST: PGFB, USPT, USOC, EPAB, JPAB, DWPI, TDBD.
STN: CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS.